

REMARKS

Reexamination and still further reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested in light of the Remarks which follow.

STATUS OF CLAIMS

Claims 1, 3-16, 20, 21, 23, 26, 27 and 29-38 remain in this application. No amendments have been made at this time.

PRIORITY

The Examiner has acknowledged the papers submitted under 35 U.S.C. § 119(a)-(d). It would be appreciated if the Examiner would make the proper entries on the Office Action Summary Sheet by marking boxes 12), a) and 3. The copy of the certified copy of the French priority document was provided by the International Bureau in the national phase case.

PREVIOUS REJECTION

Applicants thank the Examiner for withdrawing the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Fanara et al. U.S. Patent No. 6,464,987 in view of Luo et al., applicants' arguments having been considered and found persuasive.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1, 3-16, 20, 21, 23, 26, 27 and 29-38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Fanara et al. U.S. Patent No. 6,464,987 in view of El-Nokaly et al. U.S. Patent No. 5, 843, 407. Applicants submit that this newly made rejection is untenable and should be withdrawn.

The subject matter of Claim 1 of the present application, which is the only independent claim herein, is a heat-sensitive composition in liquid form, comprising

- a hydrophobic organic liquid,
- an organogelling substance which is an amino acid derivative, the molecules of which have the capacity to bind together via bonds of low energy, and
- a bioactive substance,

which changes to the organogel form during its administration to an animal body and remains in gel form at the body temperature of said animal body.

Hence, the composition of the invention is under liquid form, and not under a gelled form, although it contains "an organogelling substance". This is due to the fact that said organogelling substance chosen in the invention is "heat-sensitive," i.e., changes from the liquid state to the gel state as a function of the temperature (page 1, lines 25-26 of the original specification). Hence, the gelation of the liquid composition can be induced by cooling the site of application of the composition (page 9, lines 2-5 of the original specification).

Fanara et al. also disclose fluid pharmaceutical compositions for controlled release of active substance. However, these compositions contain phospholipids as organogelling substances. Fanara et al. do not teach any organogelling substance which is an amino acid derivative.

Furthermore, the compositions taught by Fanara et al. are not heat-sensitive because they are able to gellify *in situ* by absorption of the surrounding aqueous phase. Contrary to what the Examiner proposes, Fanara et al.'s compositions will not have a transition temperature from liquid to gel lower than the temperature of the site of the injection; that is, cooling Fanara's compositions will certainly not result in their gellification, since the gellification process of Fanara et al.'s compositions relies on *in vivo* absorption of fluids and not on changes in temperature. On the contrary, cooling the "heat-sensitive" composition of the present invention triggers its gellification (cf. Figure 1, for example, of the as-filed specification).

Thus, a man skilled in the art should absolutely not follow Fanara et al.'s teaching in order to realize the present invention.

To have the idea to use an amino acid derivative as the organogelling substance in their composition, the present inventors had to know that the amino acid derivative:

- 1) is compatible with *in vivo* administration,
- 2) is a heat-sensitive component (i.e. liquid at room temperature to be injectable and gellified after cooling to form an implant), and
- 3) can liberate bioactive substances.

None of these elements have been described or even suggested by El-Nokaly et al., the secondary reference.

As a matter of fact, the El-Nokaly et al. patent relates to lipstick compositions which comprise a gelling agent selected from the group consisting of hydrophobic silicas, hydrophobic clays with an effective amount of an activator, propylene carbonate, ethyl cellulose, n-acyl amino acid amides and n-acylamino acid esters and mixtures thereof. (col. 5, lines 10-14). The N-acyl amino acid derivatives are taught to be prepared from glutamic acid, alanine, lysine, glutamine, aspartic acid and mixtures thereof, (col. 7, lines 41-47). Preferred gelling agents are taught to be n-acyl glutamic acid amides and n-acyl glutamic acid esters of a particular structure (col. 7, lines 45-62). The patent goes on to name a number of specific gelling agents of this type, which are referred to as preferred secondary gellants (col. 7, line 64 to col. 8, line 14). Every specific gelling agent named there is an amide of glutamic acid. The only specific gelling agent of this type exemplified in the patent is N-lauroyl-L-glutamic acid-di-n-butyl amide, which is named as the gelling agent in Examples VII and VIII. While applicants' "amino acid derivative" in Claim 1 is broad enough to encompass El-Nokaly et al.'s n-acyl amino acid amides or esters, and applicants' "alanine ester derivative" is broad enough to encompass El-Nokaly et al.'s amino acid esters, the cited patent neither discloses nor suggests any specific alanine ester derivatives, such as those specified in applicants' Claims 30, 31, 37 and 38. Thus, it seems particularly inappropriate for the Examiner to have included these claims in the record rejection. At any rate, the man skilled in the art only learns from El-Nokaly et al. that N-acyl amino acid derivatives can be gelling agents. However, this feature was already disclosed in several other documents previously quoted by the Examiner, in particular in Luo et al.

As in Luo et al, however, it is not mentioned or suggested in El-Nokaly et al. that amino acid derivatives are compatible with *in vivo* administration. The presence of amino acid derivatives in a lipstick composition does not mean that it is safe to be incorporated in a composition dedicated to be administered *in vivo* by injection.

Moreover, as in Luo et al., it is not taught or suggested by El-Nokaly et al. that alanine derivatives are liquid at room temperature and gellify when cooled. Indeed, lipsticks are solid compositions at room temperature, which is due to the high content of wax present in lipstick compositions (40% to 60%) and not to the 2% of amino acid derivatives potentially present in the composition.

In particular, EI-Nokaly et al. do not teach the behavior of amino acid derivatives at body temperature. It is therefore not obvious that a composition by virtue of the fact that it contains amino acid derivatives will remain in gel form at body temperature as the present composition does.

Finally, EI-Nokaly et al. teach that the inclusion of their gelling agent facilitates the retention of emollient oils particularly under high humidity and temperatures (Abstract). For example, 2% of N-lauroyl glutamic acid di-n-butyl amide is able to provide a lipstick which is sweat-resistant or sweat-free (Examples 7 and 8 and col. 25, lines 13-18), that is, which avoids the excretion of oils on to the surface of the lipstick. Hence, the EI-Nokaly et al. patent does not teach the use of amino acid derivatives to facilitate the release of bioactive substance.

Thus, EI-Nokaly et al. combined with Fanara et al. do not teach or suggest the essential features required to realize the present invention, which is therefore not obvious.

The rejections of the instant claims under 35 U.S.C. § 103(a) are thus without merit and should be withdrawn. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

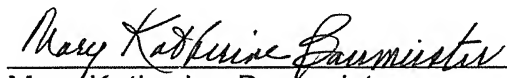
As a final point, applicants submit that the finality of the July 17, 2008 Official Action is improper and should be withdrawn. The Examiner has stated that the new rejection has been necessitated by applicants' previously submitted amendment and therefore has been made final. However, the new rejection, based on a new combination of references, is no more appropriate than the previous rejection and therefore was not necessitated by applicants' amendment. Therefore the rejection should not have been made final.

Respectfully submitted,

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